Mechanism-Based Facilitated Maturation of Human Pluripotent Stem Cell-Derived Cardiomyocytes.

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Public Summary:
Abstract BACKGROUND: Human embryonic stem cells (hESCs) can be efficiently and reproducibly directed into cardiomyocytes (CMs) using stage-specific induction protocols. However, their functional properties and suitability for clinical and other applications have not been evaluated. METHODS AND RESULTS: Here we showed that CMs derived from multiple pluripotent human stem cell lines (hESC: H1, HES2) and types (induced pluripotent stem cell) using different in vitro differentiation protocols (embryoid body formation, endodermal induction, directed differentiation) commonly displayed immature, proarrhythmic action potential properties such as high degree of automaticity, depolarized resting membrane potential, Phase 4- depolarization, and delayed after-depolarization. Among the panoply of sarcolemmal ionic currents investigated (I(Na)(+)/I(CaL)(+)/I(Kr)(+)/I(NCX)(+)/I(f)(+)/I(to)(+)/I(K1)(-)/I(Ks)(-)), we pinpointed the lack of the Kir2.1-encoded inwardly rectifying K(+) current (I(K1)) as the single mechanistic contributor to the observed immature electrophysiological properties in hESC-CMs. Forced expression of Kir2.1 in hESC-CMs led to robust expression of Ba(2+)-sensitive I(K1) and, more importantly, completely ablated all the proarrhythmic action potential traits, rendering the electrophysiological phenotype indistinguishable from the adult counterparts. These results provided the first link of a complex developmentally arrested phenotype to a major effector gene, and importantly, further led us to develop a bio-mimetic culturing strategy for enhancing maturation. CONCLUSIONS: By providing the environmental cues that are missing in conventional culturing method, this approach did not require any genetic or pharmacological interventions. Our findings can facilitate clinical applications, drug discovery, and cardiotoxicity screening by improving the yield, safety, and efficacy of derived CMs.

Scientific Abstract:
BACKGROUND: -Human embryonic stem cells (hESCs) can be efficiently and reproducibly directed into cardiomyocytes (CMs) using stage-specific induction protocols. However, their functional properties and suitability for clinical and other applications have not been evaluated. METHODS AND RESULTS: -Here we showed that CMs derived from multiple pluripotent human stem cell lines (hESC: H1, HES2) and types (induced pluripotent stem cell or iPSC) using different in vitro differentiation protocols (embryoid body formation, endodermal induction, directed differentiation) commonly displayed immature, pro-arrhythmic action potential (AP) properties such as high-degree of automaticity, depolarized resting membrane potential (RMP), Phase 4- depolarization and delayed after-depolarization (DAD). Among the panoply of sarcolemmal ionic currents investigated (I(Na)(+)/I(CaL)(2+)/I(Kr)(+)/I(NCX)(+)/I(f)(+)/I(to)(+)/I(K1)(-)/I(Ks)(-)), we pinpointed the lack of the Kir2.1-encoded inwardly rectifying K(+) current (I(K1)) as the single mechanistic contributor to the observed immature electrophysiological properties in hESC-CMs. Forced expression of Kir2.1 in hESC-CMs led to robust expression of Ba(2+)-sensitive I(K1) and more importantly, completely ablated all the pro-arrhythmic AP traits, rendering the electrophysiological phenotype indistinguishable from the adult counterparts. These results provided the first link of a complex developmentally arrested phenotype to a major effector gene, and importantly, further led us to develop a bio-mimetic culturing strategy for enhancing maturation. CONCLUSIONS: -By providing the environmental cues that are missing in conventional culturing method, this approach did not require any genetic or pharmacological interventions. Our findings can facilitate clinical applications, drug discovery and cardiotoxicity screening by improving the yield, safety and efficacy of derived CMs.